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The Influence of Different Metabolic Syndrome Definitions in Predicting Vasculogenic Erectile Dysfunction - Is there a Role for the Index of Central Obesity ?

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Mestrado Integrado em Medicina

Área: Urologia

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Doutor Nuno Tomada

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
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Dedication

As one man shapes his work, he is, himself, intimately shaped by the ones more close to him. In that sense, this work would not be possible without the skilful handcraft of a few sculptors. To my family, my girlfriend and my closest friends I dedicate this sober sculpture.

The Influence of Different Metabolic Syndrome Definitions in Predicting Vasculogenic Erectile Dysfunction: Is there a Role for the Index of Central Obesity?

Short title: ICO & ED

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Summary

Aims: analyze ICO´s capacity in predicting hemodynamic impairment in Erectile Dysfunction (ED) patients, independently and integrated in Metabolic Syndrome (MetS) definitions.

Methods: 485 ED patients followed in Urology consult from 1/2008 until 3/2012 were evaluated by a standardized protocol: health questionnaire, anthropometric measurements (AM), blood pressure and analysis, and Penile Duplex Doppler Ultrasound (PDDU) exam. Associations between AM and MetS definitions, including ATPIII, IDF and a new definition replacing Waist Circumference (WC) by ICO in ATPIII MetS definition (ModATPIII), and PDDU were calculated.

Results: ICO was the measure of obesity more strongly correlated with diminished mean Peak Systolic Velocity (mPSV) (r=-0.189, $P<0.001$). A positive association remains when replacing WC by ICO≥0.60 in ATPIII MetS definition (ModATPIII). With ModATPIII, prevalence of MetS was 32.4%, 49.2% of these patients having Arterial Dysfunction (AD) in PDDU. Patients with ModATPIII had lower mPSV when compared to non-MetS patients (30.8 vs. 37.1, $P<0.001$).

Only the IDF definition had a significant association with AD (OR=1,853 [95%CI: 1.202–2.857]).

Conclusions: ICO revealed potential value to predict PDDU changes in a MetS context. However, IDF definition presented a stronger correlation with arteriogenic ED. Although longitudinal studies are necessary to confirm this hypothesis, our study highlights the importance of different MetS definitions for ED assessment.

Keywords: Erectile Dysfunction; Index of Central Obesity; Metabolic Syndrome; Penile Hemodynamics; Penile Duplex Doppler Ultrasound;

Introduction

Erectile dysfunction (ED) is the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance. [1] Being mostly vasculogenic in nature, mainly due to aging or underlying co-morbidity, ED can be seen as a clinical manifestation of a functional or structural abnormality that affects penile circulation and that is part of a more generalized vascular dysfunction. [2,3] This underlying concept is illustrated by a positive association of ED with Metabolic Syndrome (MetS), which has been shown to triple its risk. [3,4,5]

The MetS, present in 27.5% of the Portuguese population[6], is defined as a set of cardiovascular risk factors such as obesity, insulin resistance, high blood pressure (HBP) and dyslipidemia, and can be seen as a low-grade chronic inflammatory state that leads to endothelial dysfunction and, in a sexual medicine context, hypogonadism. [5] Many definitions exist for it, being National Cholesterol Education Program – Adult Treatment Panel III (ATPIII) and International Diabetes Federation (IDF) the most used ones, with ATPIII having a reported superior correlation with penile blood flow impairment, low testosterone and Cardiovascular Events. [5,7] Therefore, it has received worldwide appraisal for its utility as a screening tool in patients with risk for events of cardiovascular nature. [8,9]

From all the components of MetS, obesity (measured by bioimpedance) and HBP are the ones that are independently associated with a deterioration of the hemodynamic profile in Penile Duplex Doppler Ultrasound (PDDU) measurements. [10] Although visceral obesity is known to play a primordial role in the pathophysiology of MetS and ED, it is also the center of some dispute concerning its overvaluation in MetS definitions. [5] This way, having none of the actual MetS

definitions considered to take visceral obesity properly into account, many new measures have been proposed for its evaluation, being Index of Central Obesity (ICO) one of the most acclaimed, as it has been shown to supplant the limitations of the traditionally used Waist Circumference (WC), namely by not neglecting height variation in subjects. [11,12]

The correlation of ICO with ED, specifically with hemodynamic changes in vasculogenic ED, has not been yet tested. Thus, this study aims to analyze the capacity of ICO in predicting hemodynamic impairment in patients with ED, either independently, or integrated in the more commonly used MetS definitions.

Patients and Methods

The present study is of transversal, descriptive and analytical nature. The sample includes patients followed in our Urology consult for ED (n=485) from January 2008 until March 2012, date of the start of the analysis. Signed informed consent on the inclusion of their data in this study was obtained for all patients. Exclusion criteria were the presence of any of the following conditions: history of recent coronary artery disease, neurological disease, pelvic trauma, major psychiatric disorder, thyroid disease, hepatic disease, end-stage renal disease, and history of drug abuse.

All patients were submitted to a standardized evaluation protocol that included a health questionnaire, physical examination, blood analysis and PDDU exam. The Health questionnaire contemplated past medical history, cardiovascular and metabolic risk factors such as High Blood Pressure (HBP), Diabetes *mellitus*, and Total cholesterol (TCho), Low-Density Lipoprotein (LDL), Triglycerides (TG) and/or High-Density Lipoprotein (HDL) abnormalities. Pharmacological history was also collected, along with alcohol and tobacco use. Physical examination was performed by the same technician and with patients barefoot and with light clothing. It contemplated systolic and diastolic blood pressure evaluation and the recording of the anthropometric parameters weight, height and WC. WC measurement was obtained using an anthropometric tape (to the nearest 0.1 cm) at the end of normal expiration at the level of the midpoint between the lower end of the 12^{th} rib and upper end of iliac crest. Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters, and ICO by dividing WC by height, both in centimeters.

The systolic and diastolic blood pressures were measured in the right arm using an automatic manometer (DINAMAP® Procare 300, GE, UK) in the sitting position after a 10-minute rest period. HBP was defined as present if arterial blood pressure was equal or over 130/85 mmHg.

Blood analysis was performed from samples of venous blood collected between 8 and 10 am after a 12-hour overnight fasting period, and the following measurements were made by routine laboratory methods: blood glucose, HDL, LDL, TG, TCho. Patients were then classified according to three MetS definitions: ATPIII, IDF and a Modified ATP III (ModATPIII) definition. Presence of MetS according to ATPIII was considered if 3 or more of the following 5 conditions were present: WC >102cm; TG >1.7 mmol/L (150 mg/dL) or anti-hypertriglyceridemic medication; HDL <1.03 mmol/L (40 mg/dL) or HDL directed medication; plasma glucose ≥6.1 mmol/L (110 mg/dL); arterial blood pressure ≥130/85 mmHg or treatment for previously diagnosed HBP. [13] MetS according to IDF was considered if central obesity (WC >94cm or BMI ≥30 Kg/m^2) was present along with 2 of the following 4: TG >1.7 mmol/L or anti-hypertriglyceridemic medication; HDL <1.03 mmol/L or HDL directed medication; plasma glucose >5.6 mmol/L (100 mg/dL); systolic blood pressure ≥130 mmHg or Diastolic blood pressure ≥85 mmHg or treatment for previously diagnosed HBP. [14] MetS according to our ModATP III was derived from ATPIII definition by substitution of the criterion WC>102cm for ICO≥0.60. ICO was calculated using the formula ICO = WC (cm) / Height (cm), and the adopted cut-off of ≥0.60 was based on National Portuguese ICO values provided by Portuguese Society of Cardiology, based on a near 17,000 individual representative anthropometric nation-wide study. [15]

PDDU examination was performed by the same investigator using the protocol suggested by the International Society for Sexual Medicine Standards Committee in *Standard Practice in Sexual Medicine* [1]. A 12 MHz transducer (GE Logic 7 Ultrasound System, UK) was used to record

penile vascular flow patterns 5, 10 and 20 minutes after the injection of 10 to 20 mcg of commercial E1 Prostaglandin (Caverject®). Before and in-between evaluations, patients were left alone to prevent disturbances and consequent loss of sexual arousal, and asked to maintain the best possible erection by tactile stimulation. The mean values of Peak Systolic Velocity (mPSV), End-Diastolic Velocity (mEDV) and Resistive Index (RI) (accordingly to the formula: RI=(PSV-EDV)/PSV) were obtained from spectral waveform measurements. The classification criteria was the following: normal for mPSV >35 cm/s, EDV <5 cm/s and RI >1; arterial insufficiency for mPSV ≤35 cm/s; mPSV asymmetry for an asymmetry in mPSV >10 cm/s; cavernous venous-occlusive disease for mPSV ≥35 cm/s and EDV ≥5 cm/s; mixed when 35> PSV >25 cm/s and EDV ≥5 cm/s. Finally, the degree of erectile response was classified according to a graded scale: 0 (no response); 1 (minimal tumescence and no rigidity); 2 (moderate tumescence and no rigidity); 3 (full tumescence and moderate rigidity); 4 (full rigidity).

Statistical analysis

The differences between the groups were assessed by unpaired Student's t-test or Mann–Whitney U-test as appropriate for continuous variables. Multivariate analysis was performed by multivariate linear regression and multivariate logistic regression for continuous and categorical dependent variables, respectively. Odds ratio (OR) with respective 95% confidence intervals (95% CI) were calculated to evaluate the association of categorical variables. Pearson correlation was performed to evaluate the association between continuous variables. Statistical analysis was performed using SPSS® version 17.0 for Windows® (SPSS Inc., Chicago, IL, USA). The software handled missing data automatically. Statistical significance was considered at *P*-level < 0.05.

Results

The population in study (n=485) had a mean age of 55.8 ± 11.1 years, mean weight of 79.9 ± 13.3 Kg and a mean height of 1.7 ± 0.1 meters (mean BMI of 27.7 ± 4.2 Kg/m^2). Mean ICO and WC were of 0.60 ± 0.07 and 101.9 ± 10.6 cm, respectively. More data about the participants is presented in **table I**.

PDDU was normal in 30.8% of patients. Arterial Dysfunction (AD), veno-occlusive dysfunction, arterial dysfunction by cavernous arteries asymmetry and mixed dysfunction were identified in 41.0%, 14.7%, 7.7% and 5.8%, respectively. MetS according to ATPIII criteria was identified in 31.1% of the population, 48.4% of it having AD diagnosed with PDDU. On the other hand, IDF MetS criteria were identified in 46.5% of patients, 49.7% of them having AD diagnosed with PDDU. Finally, using ModATP III, the prevalence of MetS was of 32.4%, 49.2% of these having AD diagnosed with PDDU. The agreement (overlap) between MetS definitions was calculated, and the results are presented in **table II**.

Patients with ATPIII and IDF MetS criteria had significantly lower mPSV comparatively to non-MetS patients (30.9 vs. 37.3 cm/s, $P<0.001$; 31.2 vs. 39.3 cm/s, $P<0.001$, respectively). Similarly, patients with ModATP III MetS criteria had significantly lower mPSV when compared to non-MetS patients (30.8 vs. 37.1, $P<0.001$) (**Fig. 1**). None of the three MetS definitions showed association with mean Peak Diastolic Velocity or RI changes on PDDU (data not shown).

Multivariate analysis including the variables HBP, Hypertriglyceridemia (HTG) (serum level of TG >1.7mmol/L / 150mg/dl), fasting glucose >5.6 mmol/L (100 mg/dL), HDL <1.03 mmol/L, BMI ≥30 Kg/m2 and WC >94 cm, showed that only HBP was independently associated with diminished mPSV on PDDU examination ($P=0.005$) (**Table III**).

In another model where ICO substituted for BMI, ICO and WC were also found to be independently associated with diminished mPSV on PDDU examination (P=0.017 and P=0.046, respectively) (**Table III**).

ICO, when compared to WC, was found to be the measure of obesity more strongly correlated with diminished mPSV on PDDU (r=-0.189, P<0.001 vs. r=-0.147, P=0.003, respectively).

An ICO over the established cut-off of 0.60 was found in 51.9% of patients. Of these, 46.0% had AD on Doppler measurements. The calculated OR for having AD in PDDU when having ICO≥0.60 was of 1.471 (95% CI: 0.986-2.194). The different MetS definitions (ATPIII, IDF and ModATPIII) were all found to be independent predictors of diminished mPSV in PDDU measurements (P=0.007, P=0.002 and P=0.008, respectively) after adjustment to age, tobacco use and TCho. Again, no association was found regarding EDV or RI alterations in this multivariate analysis.

When comparing the three definitions in their correlation with AD in PDDU, IDF was found to have the only statistically significant OR (1,853 [95% CI: 1.202-2.857]). MetS ATPIII and ModATP III presented OR of, respectively, 1.507 (95% CI: 0.983-2.310) and 1.534 (95% CI: 0.992-2.374).

Discussion

Due to the existence of several MetS definitions, their specificity, sensibility and prediction capability of different pathological outcomes has been widely and thoroughly studied, but their clinical impact is still controversial. In the particular setting of vasculogenic ED, different definitions have been studied and ATPIII has been found to be the one that showed the strongest correlation with diminished mPSV in PDDU measurements. [7] In our study, such conclusion was not verified as ATP III, IDF and ModATP III definitions were all found to be positively correlated with diminished mPSV after adjustment for confounding factors. However, from the 3 definitions, IDF was the one that showed an independent association with mPSV with the highest statistical significance (P=0.002; vs P=0.007 in ATPIII and P=0.008 in ModATPIII) and the only one to show a statistically significant association with AD.

The IDF's superior correlation with Arteriogenic ED, although not consistent with the findings of Corona and colleagues, corroborates the results of other studies that show a superior correlation of IDF with pathological cardiovascular alterations such as carotid atherosclerosis and arterial stiffness. [7,16,17] Thus, these results constitute an upgrade on the already polemical comparison between MetS definitions, where studies repeatedly show conflicting results.

Although visceral obesity has been shown to be, when compared to subcutaneous and generalized obesity, the one that mostly determines the deleterious effects of MetS such as ED, the most used MetS definitions (ATPIII and IDF) do not evaluate it properly and also disregard interindividual anthropometric variations such as height. [11,12,18,19]. Different anthropometric parameters of visceral obesity have been analysed in the context of ED, although few studies have been done to test these parameters in the specific setting of hemodynamic alterations in PDDU. [18] In fact,

Riedner and colleagues have found that the anthropometric indicators of visceral obesity more associated with ED diagnosed by clinical history in a Brazilian population were sagittal abdominal diameter, sagittal abdominal diameter-height index, waist-hip ratio, WC >106 cm and WC >102 cm. [18] Of these, the latter was found to be the strongest predictor of ED. However, when evaluating the predictive value of hemodynamic changes in PDDU, WC >102 cm failed to show such an independent association. [10] This way, although WC is the visceral obesity measure most used in clinical practice and in the definitions of MetS, its limitations in evaluating short-stature individuals suggest that it may also not be the more appropriate or predictive measure when evaluating penile hemodynamic changes in ED patients. [7,12,20] ICO, a nouvelle anthropometric measure, has been proposed not only as a more accurate measure in the evaluation of central obesity but also as a more accurate substitute of WC in MetS definitions. [8] Although having been positively correlated with insulin resistance and hypogonadism, no studies have been done so far to test its utility in ED.

In this study, we have found that ICO (with a cut-off of 0.60 defined by the national median) was correlated with diminished mPSV in PDDU measurements, but the same has been found for WC and BMI although with less significant results. In a statistical model including factors such as HBP, HTG, HDL levels, WC, ICO and insulin resistance, only HBP and the anthropometric parameters ICO and WC >94cm have been shown to be independently associated with a diminished mPSV on PDDU measurements. ICO over 0.60 represented a 47% chance of detecting hemodynamic changes in PDDU exam in patients with diagnosed ED.

Such results corroborate the findings of Tomada and colleagues regarding HBP, but also highlight the positive correlation of hemodynamic alterations in ED with an anthropometric parameter which, as far as we know, has not yet been done. [10] However, contrarily to this previous study,

WC was also found to be independently associated with diminished mPSV. This positive correlation can be partly explained by the fact that a lower cut-off was used (94cm vs 102cm).

In spite of such positive association, one must point out that the sole nature of an anthropometric parameter makes this correlation liable to potential confounding factors, such as morphologic differences between individuals. Thus, iatrogenic (p.e., corticosteroids) and pathological changes on fat distribution must also be considered when anthropometrically evaluating an individual.

Taking into account the positive correlation of both WC and ICO with penile AD, ICO revealed to be more strongly associated with diminished mPSV on PDDU. Bearing in mind the positive associations of ICO with penile hemodynamic changes, our study suggests that ICO might be more appropriate than the traditional WC in predicting hemodynamic changes when evaluating patients with ED. This finding is especially useful in populations in which there is a higher prevalence of individuals of short stature, which are especially prone to adverse cardiovascular events and whose central obesity is not correctly evaluated by WC. [19,21] In fact, in patients with short stature, WC is not the best way to infer visceral obesity, as it may be increased due to the decreased height of the subject. This is also valid in the elderly population, in which there is a decrease of height with age. ICO also outstands WC on the strength of correlation with insulin resistance, while simultaneously maintaining its simplicity of calculation. [8]

The transversal nature of this study and the fact that the study only included patients with ED does not allow us to state that ICO is a predictive measure of ED. Indeed, although it is proposed as a more accurate measure of visceral obesity, further representative longitudinal studies comparing the different visceral obesity measures are necessary to clarify this question. [12]

Concerning the adopted ICO cut-off value, it is possible to observe that our study´s median ICO and national-based ICO are similar (0.60). This proximity is maintained not only when sub-

analyzing the national data in the 50-59 age group (in which this study's median age is included), but also at a district level. In fact, 50-59 age group ICO´s values were exactly the same as the entire adult population (0.60), and the Porto´s district value was of 0.59. Although the national ICO was obtained from a statistically representative nation-wide population, it is not completely correct to present it as a national cut-off as it was obtained from a primary health-care seeking population. Thus, it might be an overestimation of national values, and hence its proximity to our ED population´s ICO. Indeed, when comparing our ICO cut-off to the ones suggested by Parikh and colleagues for other Mediterranean countries based on WC cut-offs suggested by IDF, one can notice that our proposed Portuguese population´s ICO is above of the values for these countries (ex: Spain: 0.54; Italy: 0.53), which have rather similar genetics and eating habits. [12,22,23] On the other hand, it is rather proximal to USA and Canada values (0.58). Nevertheless, one must note that these countries' suggested ICO was not based on the measurement of height and WC by a single study, but rather on the conjugation of separate results by different studies. Therefore, data may not be correct at the individual level. This cut-off seeking limitation is one of the principal difficulties of ICO usage, as pointed out by Parikh and colleagues. [12] Despite the discussion about the ICO´s cut-off value, it is clear that when analyzed as a continuous variable it has an important correlation with mPSV.

In conclusion, ICO has been shown to be the measure of obesity more strongly correlated with hemodynamic changes in Penile Doppler Measurements. Its integration in the traditional MetS definitions has also been shown to be associated with penile hemodynamic changes in an ED setting.

In spite of such association, the integration of ICO in the MetS definition has not been found to increase the prediction capability of Penile Hemodynamic results compared to the traditional MetS definitions. Other studies are necessary to confirm these findings.

Declaration of interest

The authors report no declarations of interest.

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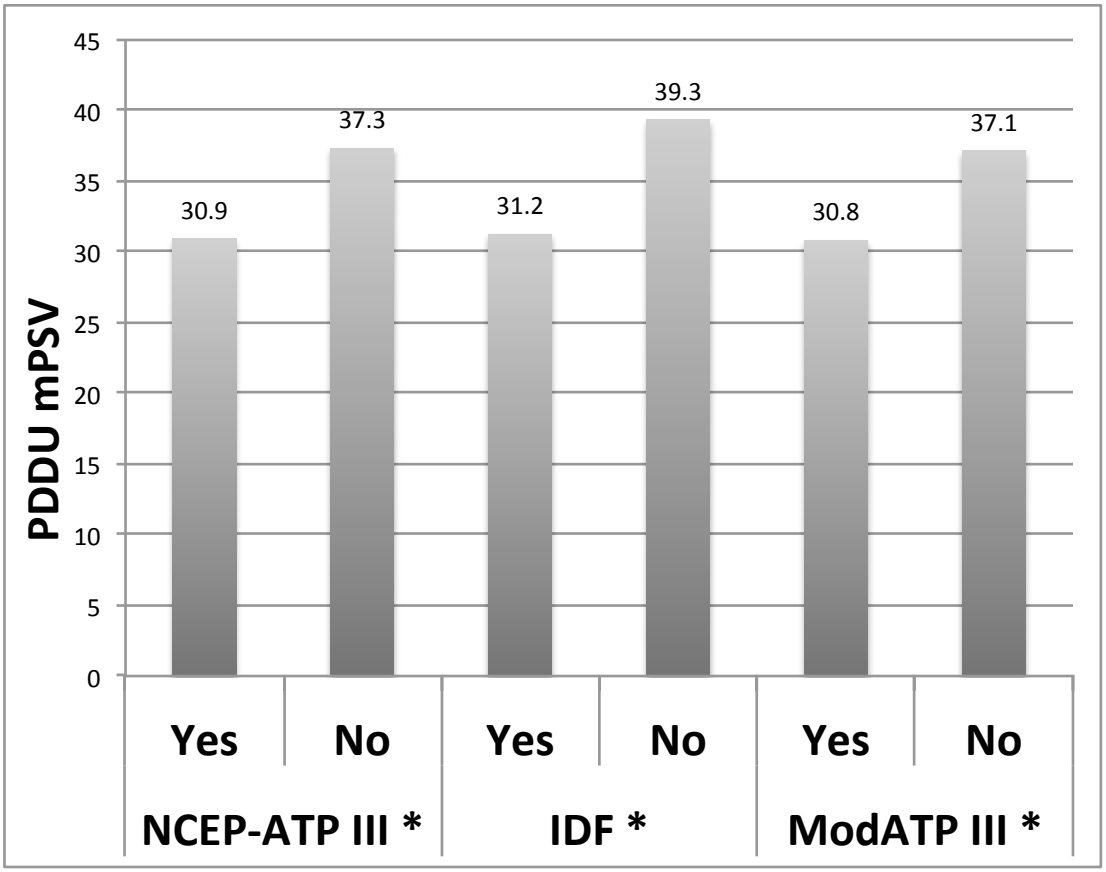
Anexos

I – Figure 1



Title and Caption:

Figure 1 – Penile Doppler Duplex Ultrasound mean Peak Systolic Velocity with/without diagnosis of Metabolic Syndrome using different definitions.

* - P< 0.001

NCEP-ATP III = National Cholesterol Education Program - Adult Treatment Panel III; ModATP III – Modified definition of National Cholesterol Education Program - Adult Treatment Panel III; IDF = International Diabetes Federation; PDDU mPSV – Penile Duplex Doppler Ultrasound mean Peak Sistolic Velocity

II – Tables

Table I – Description of the population in study.

Variable	Description	Value
Total population (n)		485
Age (years)		55.8 ± 11.1
Weight (Kg)		79.9 ± 13.3
Height (meters)		1.7 ± 0.1
WC (centimeters)		101.9 ± 10.6
ICO	ICO = WC (cm) / Height (cm)	0.60 ± 0.07
BMI (Kg/m^2)		27.7 ± 4.2
IIEF-5 Score		11.7 ± 4.7
Metabolic Syndrome (NCEP-ATPIII Criteria) (%)		31.1
Metabolic Syndrome (IDF Criteria) (%)		46.5
Metabolic Syndrome (Modified NCEP-ATPIII) (%)		32.2
Metabolic Syndrome Components (%)	HBP (≥ 130/85mmHg) or treatment	49.3
	Hypertriglyceridemia (≥1.7 mmol/L; 150 mg/dL;)	29.6
	Insulin Resistance (ATP III) (≥6.1 mmol/L / 110 mg/dL)	33.9
	Insulin Resistance (IDF) (>5.6 mmol/L / 100 mg/dL)	78.5
	Low HDL (<1.03 mmol/L; 40 mg/dL)	25.4
	WC (ATP III) > 102 cm	52.1
	WC (IDF) > 94 cm / BMI ≥ 30	80.1 / 23.0

Tobacco (%)	Smoker	23.3
	Ex-Smoker	33.5
	Non-Smoker	43.2
Current Medication (%)	Anti-Aggregant Agent	27.5
	Beta-Blocker	17
	AR Blockers	17.2
	ACE Inhibitors	22.5
	Calcium Channel Blockers	16.5
	Thyazidic Diuretics	16.7
	Antidepressants	9.5
	Benzodiazepines	18
	Statins	36.2
	Nitrates	4.7
	Fibrates	7
	Warfin	3.1
Penile Curvature (%)		8

Data are expressed as mean ± standard deviation when in normal distribution and as percentage when categorical.

ICO = Index of Central Obesity; BMI = Body Mass Index; IIEF-5 = Abridged 5-item version of the International Index of Erectile Function; ATP III = National Cholesterol Education Program - Adult Treatment Panel III; ModATP III = Modified definition of National Cholesterol Education Program - Adult Treatment Panel III; IDF = International Diabetes Federation; HBP = High Blood Pressure; HDL = High-density Lipoprotein; AR = Angiotensin Receptor; ACE = Angiotensin-Converting Enzyme; WC = Waist Circumference.

Table II – Overlap between different MetS definitions.

MetS Definition	Positive Concordance IDF (%)	Negative Concordance IDF (%)	Positive Concordance ModATP III (%)	Negative Concordance ModATP III (%)
ATP III	75.4	98.5	89.9	97.4
ModATP III	96.9	81.7		

MetS = Metabolic Syndrome; ATP III = National Cholesterol Education Program - Adult Treatment Panel III; ModATP III = Modified definition of National Cholesterol Education Program - Adult Treatment Panel III; IDF = International Diabetes Federation.

Table III – Multivariate analysis to evaluate the independent association of the Metabolic Syndrome criteria to a diminished mean Peak Systolic Velocity (mPSV) on Penile Doppler Duplex Ultrasound (PDDU) examination.

Model 1			**Model 2**		
Variable	**Beta Coefficient**	***P* value**	**Variable**	**Beta Coefficient**	***P* value**
HBP (>130/85mmHg)	-0.214	0.005	HBP (>130/85mmHg)	-0.190	0.012
Hypertriglyceridemia (>1.7 mmol/L)	-0.027	0.726	Hypertriglyceridemia (>1.7 mmol/L)	-0.038	0.615
Fasting Glucose (>5.6 mmol/L)	-0.087	0.236	Fasting Glucose (>5.6 mmol/L)	-0.073	0.318
HDL (<1.03 mmol/L)	0.004	0.962	HDL (<1.03 mmol/L)	0.000	0.995
BMI over 30	-0.086	0.253	ICO ≥ 0.60	-0.210	0.017
WC > 94 cm	0.081	0.286	WC > 94 cm	0.173	0.046

HBP = High Blood Pressure; HDL = High Density Lipoprotein; BMI = Body Mass Index; ICO = Index of Central Obesity

Model 1 – Multivariable analysis testing independent association of 6 different variables with diminished Mean Peak Systolic Velocity (mPSV) in Penile Doppler Duplex Ultrasound.

Model 2 - Multivariable analysis model based on Model 1, with substitution of BMI for ICO.

III – Publishing Guidelines

Consult in following pages.

IV – Strobe Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both

		direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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